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Prognostic Value of Exercise Thallium-201 Imaging Performed Within 2 Years of Coronary Artery Bypass Graft Surgery

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Objectives. **We sought to determine the prognostic capabilities of exercise thallium (Tl)-201 tomographic imaging performed relatively early (within 2 years) after coronary artery bypass graft surgery (CABG).**

Background. **Exercise testing is commonly performed after CABG, but few data exist demonstrating its prognostic value in this setting.**

Methods. **Four hundred eleven patients were followed up for a median duration of 5.8 years. Eleven prospectively chosen clinical, exercise and Tl-201 variables were tested for their associations with outcome end points by means of proportional hazards regression models.**

Results. **During follow-up there were 60 deaths from any cause, 53 initial cardiac deaths or nonfatal myocardial infarctions (MIs) and 22 late (>3 months after the Tl-201 study) revascularization procedures. The number of abnormal Tl-201 segments on the postexercise image was the only variable in the multivariate analyses to show a significant association with all three outcome end points: chi-square 7.3, p = 0.007 for overall mortality; chi-square 8.1, p = 0.004 for cardiac death or MI; chi-square 7.8, p = 0.005 for any cardiac event. Other independent predictors of outcome were exercise duration (chi-square 10.7, p = 0.001) and age (chi-square 3.9, p = 0.049) for overall mortality and exercise angina score (chi-square 8.7, p = 0.003) for cardiac death or MI. The 5-year survival rate free of cardiac death or MI was 93% for patients without angina and a normal image or small postexercise perfusion defect versus 71% for patients with angina and a medium or large defect.**

Conclusions. **Exercise Tl-201 imaging performed within 2 years of CABG can stratify patients into low and high risk subgroups.**

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According to the American College of Cardiology/American Heart Association Guidelines for Clinical Cardiac Radionuclide Imaging (1), myocardial perfusion imaging after coronary artery bypass graft surgery (CABG) is considered a class I indication (usually appropriate and considered useful) for assessment of ischemia in symptomatic and selected asymptomatic patients. An abundance of data demonstrates that conventional exercise testing and exercise thallium (Tl)-201 imaging can be used to document improvement in myocardial ischemia after CABG and to detect bypass graft stenosis (2–9). However, there are very few published data examining the prognostic value of exercise testing after CABG (10–15). The studies using conventional electrocardiographic (ECG) monitoring have reported varying results (10–12), and the only study that used Tl-201 imaging enrolled patients who had undergone CABG at least 5 years earlier (15). The purpose of the present study was to evaluate the prognostic value of exercise Tl-201 imaging performed relatively early after CABG.

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Methods

Study group. The study cohort was retrospectively identified from the Mayo Clinic Nuclear Cardiology Laboratory database. Patients were eligible for the study if they 1) performed an exercise tomographic Tl-201 test between December 1985 and December 1993; and 2) had undergone CABG within the 2 years preceding the Tl-201 study. A 2-year cut-point was selected because many patients at our institution who undergo CABG return at 1 year plus or minus a few months for follow-up evaluation, at which time a stress test may be performed. Patients were excluded from the study for the following reasons: 1) technically poor images (24 patients); 2) left bundle branch block or paced ventricular rhythm on the rest ECG (to avoid false positive perfusion defects) (16,17) (89 patients); 3) evidence of clinically significant valvular heart disease (122 patients); or 4) history of percutaneous transluminal coronary angioplasty (PTCA) before CABG (163 patients). The rationale for excluding patients with a previous PTCA was to eliminate patients whose vascular biology (and results of subsequent myocardial perfusion imaging) could be very different from patients who had not undergone previous PTCA, especially those patients in whom CABG had been performed as an emergency rescue procedure for failed PTCA.

The study group included 411 patients, whose clinical characteristics are shown in Table 1. Most but not all patients

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Abbreviations and Acronyms

CABG = coronary artery bypass graft surgery
ECG = electrocardiogram, electrocardiographic
MI = myocardial infarction
PTCA = percutaneous transluminal coronary angioplasty
Tl = thallium

had undergone CABG at the Mayo Clinic. Operative records were available for 394 patients. The mean number of vessels bypassed was three per patient. An internal mammary artery graft was used in 79% of patients. Symptom status at the time of the exercise Tl-201 test was coded according to the criteria of Diamond (18). Approximately two-thirds of the study group were symptomatic, the majority of whom had atypical angina.

Exercise tomographic Tl-201 imaging. Patients exercised according to the Bruce or Naughton protocols to traditional end points (severe fatigue, moderate angina or ≥2 mm ST segment depression). Three ECG leads were monitored continuously, and a 12-lead ECG was recorded every minute. The ECG was interpreted as positive for ischemia if there was ≥1.0-mm horizontal or downsloping ST segment depression 0.08 s after the J point.

Three to 4 mCi of Tl-201 were injected near peak exercise. After exercise a single anterior planar image was acquired for 5 min to assess cardiac size and Tl-201 lung uptake. Tomographic imaging was then performed over a 180° arc using the "step and shoot" method. Delayed imaging was repeated 4 h later. Because of a change in protocol in at our laboratory, 184 patients tested after January 1, 1990 underwent reinjection with 1 mCi of Tl-201 before delayed imaging. Images were reconstructed using a Ramp-Hanning filter and standard back-projection algorithms. Tl-201 uptake was graded subjectively in three orthogonal planes (short axis, horizontal long axis, vertical long axis) divided into 24 segments on a five-point scale (0 = absent uptake; 1 = severely, 2 = moderately, 3 = mildly decreased uptake, respectively; 4 = normal uptake) on the postexercise and delayed images displayed side by side by the consensus of two experienced observers (19,20). For the purposes of this study, only the scores of the 14 short-axis segments (4 at the apical, 5 at the mid, 5 at the basal level of the left ventricle) were used. The horizontal and vertical long-axis images were used primarily to confirm the presence of defects seen on the short-axis images and to aid in selection of the apical and basal short-axis slices when large defects involved these regions. *Redistribution* was defined as improved uptake of one grade or more. Any segment demonstrating either partial or complete redistribution was coded as redistribution. *Mild fixed defects* (score of three on both the postexercise and delayed images) were considered normal. Coronary artery distributions were assigned as previously described (20). *Ischemia proximal to bypass graft insertion* was defined as redistribution confined to a basal segment or segments without redistribution in the apical or mid segments of a coronary artery distribution. For example, a patient with redistribution in the anterior wall at the base but with either normal perfusion or a fixed defect in the anterior wall at the midlevel and apex would be coded as having ischemia proximal to bypass graft insertion. *Tl-201 lung uptake* was graded subjectively as increased or not increased on the anterior planar image. In borderline cases, lung uptake was quantified and graded as increased if the Tl-201 lung/heart count ratio was ≥0.5.

Table 1. Clinical Characteristics of 411 Study Patients

Age (yr)	62 ± 9
Men/women	80%/20%
Risk factors	
Smoking history	63%
Hypertension	48%
Hypercholesterolemia	53%
Diabetes mellitus	18%
Previous MI	46%
Time from index CABG (mo)	11 ± 7
No. of grafts*	3 ± 1
IMA graft*	79%
Symptom status	
Asymptomatic	34%
Dyspnea	7%
Chest pain	59%
Typical angina	17%
Atypical angina	38%
Noncardiac pain	5%
Antianginal medications	58%
Long-acting nitrates	20%
Beta-blockers	32%
Calcium channel blockers	34%

*Based on 394 patients for whom this information was available. Data presented are mean value ± SD or percent of patients. CABG = coronary artery bypass graft surgery; IMA = internal mammary artery; MI = myocardial infarction.

Follow-up data. Patient outcome was determined using a combination of chart review, mailed questionnaire or telephone contact. *Significant events* were defined as death, nonfatal MI and PTCA or repeat CABG. Hospital records or death certificates (or both) were obtained for patients with events to confirm the accuracy of stated events. *Deaths* were coded as cardiac or noncardiac. *Revascularization procedures* were coded as early (≤3 months of the Tl-201 study) or late (>3 months after the Tl-201 study). Follow-up was 96% complete at a median duration of 5.8 years in those patients alive at follow-up.

Statistical analysis. Three outcome end points were analyzed: 1) death from any cause (no patient censored from analysis); 2) initial cardiac death or nonfatal MI (censoring of patients with noncardiac death or PTCA/CABG at any time after the Tl-201 study); and 3) initial cardiac death, nonfatal MI or late PTCA/CABG (censoring of patients with noncardiac death or early PTCA/CABG). Eleven variables were prospectively chosen without knowledge of patient outcome to test their association with the three end points using Cox univariate and multivariate stepwise proportional hazards regression models (21). The number of variables analyzed was

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Table 2. Variables Analyzed*

Clinical	
Age	
Gender	
Previous MI	
Chest pain class	
Exercise	
Duration	
Magnitude of ST segment depression	
Angina score	
Thallium-201	
No. of abnormal segments after exercise	
Any redistribution	
No. of segments with redistribution	
Increased lung uptake	

*See text for discussion. MI = myocardial infarction.

intentionally limited to avoid "overfitting" of the models to the outcome end points. The 11 variables were selected based on their proven prognostic value in earlier studies (22,23) and are shown in Table 2. After this study began, more recent publications demonstrated the prognostic value of summed stress and reversibility scores (15,24). Post hoc analyses were performed to examine the prognostic value of these indexes, substituting the summed stress score for the number of abnormal segments after exercise and the summed reversibility score for the number of segments with redistribution. The exercise angina score was based on the criteria of Mark et al. (22). Exercise duration was expressed in metabolic equivalents (METs) and estimated from published nomograms (25). Survival curves were generated using the Kaplan-Meier method (26). For all analyses, a p value <0.05 was considered significant.

Results

Exercise Tl-201 imaging (Table 3). Exercise-induced angina and an ischemic ECG each were present in ~25% of the study group. Seventy percent of patients had an abnormal postexercise Tl-201 image. The median number of abnormal segments was three. More than 50% of patients had redistribution, but the majority had only small (one to three segments) ischemic defects. Ischemia proximal to bypass graft insertion was present in 12% of patients.

Events during follow-up (Table 4). Sixty patients died during follow-up. The 5-year overall survival rate was 88% (Fig. 1). There were 53 initial "hard" cardiac events (22 cardiac deaths, 31 nonfatal MIs). At 5 years, the survival rate free of cardiac death or MI was 87% (Fig. 2), and survival free of a hard cardiac event or late PTCA/CABG was 83% (Fig. 3).

Associations between clinical, exercise and Tl-201 variables and events. Of the 11 prospectively chosen variables for analysis (Table 2), only those that demonstrated a statistically significant association with outcome are shown (Tables 5 to 7). The single variable independently predictive of all three outcome end points was the number of abnormal Tl-201 segments on the postexercise images. Poor exercise duration and increasing age were independently predictive of total mortality, and exercise angina score was independently predictive of the end point of cardiac death or MI.

The other clinical and Tl-201 variables contained relatively little prognostic information. Besides age the only clinical variable that was independently predictive of outcome was chest pain class, which was associated with the single end point

Table 3. Exercise Thallium-201 Results in 411 Study Patients

Duration (METs)	8.0 ± 2.4
Peak heart rate (beats/min)	132 ± 24
Angina	22%
Positive electrocardiogram	29%
Abnormal postexercise image	70%
1–3 segments	27%
4–6 segments	24%
≥7 segments	18%
Redistribution	58%
1–3 segments	32%
4–6 segments	18%
≥7 segments	8%
Redistribution proximal to graft insertion	12%
Increased lung uptake	12%

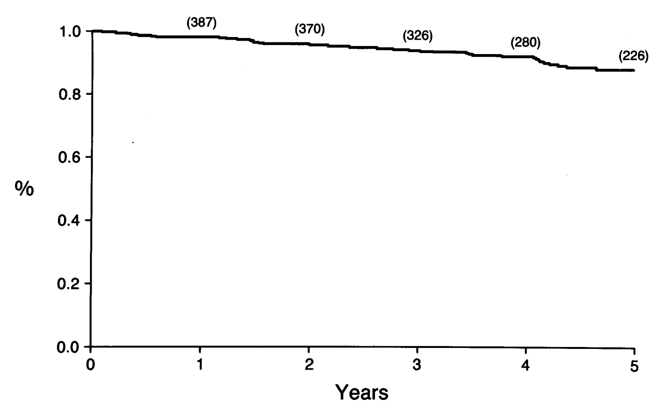
Data presented are mean value ± SD or percent of patients. METs = metabolic equivalents.

Table 4. Events During Follow-Up

Total deaths	60
Cardiac deaths	26
Initial	22
Subsequent	4
Noncardiac deaths*	34
Nonfatal MI	31
PTCA/repeat CABG	38
Early (≤3 mo)	16
Late (>3 mo)	22

*Included cancer (n = 10), stroke (n = 6), pneumonia/chronic lung disease (n = 6), end-stage renal disease (n = 2), sepsis (n = 2), cirrhosis (n = 1), gastrointestinal bleeding (n = 1), pulmonary embolus (n = 1), suicide (n = 1), trauma (n = 1), indeterminate (n = 3). PTCA = percutaneous transluminal coronary angioplasty; other abbreviations as in Table 1.

Figure 1. Kaplan-Meier curve for overall survival. See text for details.



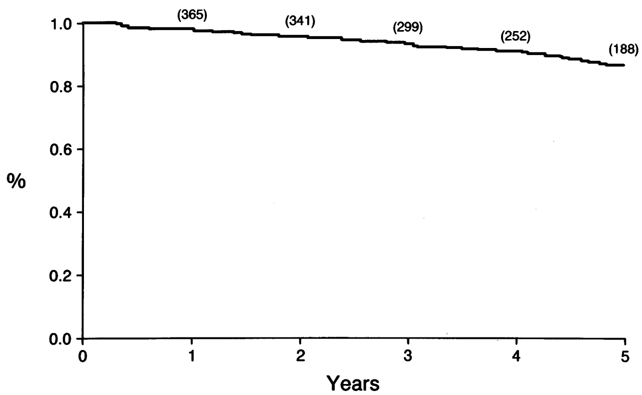


Figure 2. Kaplan-Meier curve for survival free of cardiac death or nonfatal MI. See text for details.

that included late PTCA/CABG. The number of Tl-201 segments with redistribution was significantly associated with the end point of cardiac death or MI in univariate but not in multivariate analysis. Patients who underwent Tl-201 reinjection before delayed imaging (15 events) were analyzed separately from those who did not (38 events) to examine whether reinjection could be influencing these results. The strength of the association between the number of segments with redistribution and the end point of cardiac death or MI was similar in the two groups: chi-square 4.2, $p = 0.04$ for reinjection; chi-square 3.4, $p = 0.06$ for no reinjection. Ischemia proximal to bypass graft insertion was not predictive of cardiac death or MI (chi-square <1, p = NS). Increased Tl-201 lung uptake was not predictive of any outcome end point in this study.

An additional analysis was performed to determine whether increased Tl-201 lung uptake and Tl-201 redistribution influenced clinicians' decisions to refer patients for repeat revascularization. Increased lung uptake ($p < 0.002$) and both the presence of any redistribution ($p < 0.001$) and the number of defects with redistribution ($p < 0.001$) were associated with early revascularization.

Risk stratification of study cohort. The study group could be stratified into low and high risk subsets on the basis of the prognostically important variables (dichotomized at selected cut-points). Figure 4 shows the survival curves for patients free of cardiac death or MI, classified on the basis of the absence or presence of exercise-induced angina and three or more or less than three abnormal Tl-201 segments on the postexercise images. The 5-year event-free survival rate was 93% for patients without either of the adverse prognostic variables, 83% for one variable and 71% for both variables. Figure 5 demonstrates that the extent of exercise-induced ischemia could also risk stratify the cohort. The 5-year survival rate free of cardiac death or MI was 72% for patients with a large ischemic defect versus 85% to 89% for the other subsets. Finally, for patients with normal Tl-201 images, the 5-year

Figure 3. Kaplan-Meier curve for survival free of cardiac death, nonfatal MI or late revascularization. See text for details.

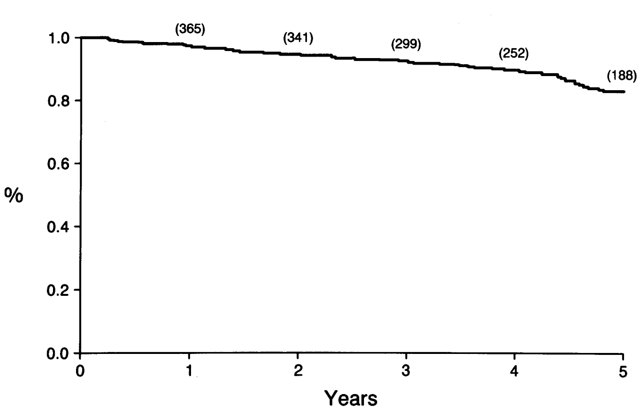


Table 5. Associations Between Clinical, Exercise and Thallium-201 Imaging Variables With Total Mortality

Variable*	Chi-Square	p Value	HR (95% CI)†
Univariate Analysis			
Shorter exercise duration	18.7	<0.001	1.30 (1.15–1.46)
Increasing age	11.6	<0.001	1.72 (1.26–2.35)
No. of abnormal Tl-201 segments after exercise	9.6	0.002	1.12 (1.04–1.20)
Multivariate Analysis			
Shorter exercise duration	10.7	0.001	1.24 (1.09–1.41)
No. of abnormal Tl-201 segments after exercise	7.3	0.007	1.10 (1.03–1.18)
Increasing age	3.9	0.049	1.40 (1.00–1.96)

*Variables not shown were not significantly associated with outcome (see text for details). †Hazard ratios (HR) for all variables are expressed for 1 unit of change (e.g., 1 metabolic equivalent [MET] or one thallium [Tl]-201 segment), except for the variable increasing age, which is expressed for each 10-year increment. CI = confidence interval.

Table 6. Associations Between Clinical, Exercise and Thallium-201 Imaging Variables With Initial Cardiac Death or Nonfatal Myocardial Infarction

Variable*	Chi-Square	p Value	HR (95% CI)†
Univariate Analysis			
Exercise angina score	10.1	0.002	1.77 (1.25–2.52)
No. of abnormal Tl-201 segments after exercise	9.3	0.002	1.13 (1.04–1.21)
No. of Tl-201 segments with redistribution	7.4	0.007	1.14 (1.04–1.26)
Shorter exercise duration	4.5	0.033	1.13 (1.01–1.26)
Multivariate Analysis			
Exercise angina score	8.7	0.003	1.69 (1.19–2.40)
No. of abnormal Tl-201 segments after exercise	8.1	0.004	1.12 (1.04–1.20)

*Variables not shown were not significantly associated with outcome (see text for details). †Hazard ratios (HR) for all variables are expressed for 1 unit of change (e.g., 1 metabolic equivalent [MET] or one thallium [Tl]-201 segment). CI = confidence interval.

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Table 7. Associations Between Clinical, Exercise and Thallium-201 Imaging Variables With Initial Cardiac Death, Nonfatal Myocardial Infarction or Late Coronary Angioplasty/Bypass Surgery

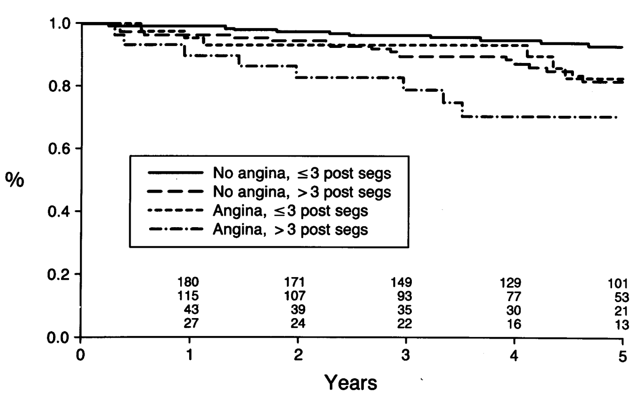
Variable*	Chi-Square	p Value	HR (95% CI)†
Univariate Analysis			
Exercise angina score	9.0	0.003	1.60 (1.18–2.19)
Chest pain class	7.4	0.007	1.33 (1.08–1.63)
No. of abnormal Tl-201 segments after exercise	6.6	0.010	1.09 (1.02–1.17)
Multivariate Analysis			
Chest pain class	8.5	0.004	1.35 (1.10–1.65)
No. of abnormal Tl-201 segments after exercise	7.8	0.005	1.10 (1.03–1.18)

*Variables not shown were not significantly associated with outcome (see text for details). †Hazard ratios (HR) for all variables are expressed for 1 unit of change (e.g., 1 metabolic equivalent [MET] or one thallium [Tl]-201 segment). CI = confidence interval.

event-free survival rate was 92%, yielding an annual hard cardiac event rate of ~1.6%.

Post hoc analysis. Table 8 shows the univariate associations between the summed stress and reversibility scores and the outcome end points and the multivariate models that were created by substituting the summed stress score for the number of abnormal segments after exercise and the summed reversibility score for the number of segments with redistribution. By univariate analysis, the chi-square values for the summed variables were modestly higher than those of the corresponding variables in the original univariate models. Additionally, the summed reversibility score was significantly associated with the end point of cardiac death, MI or late PTCA/CABG, whereas the number of segments with redistribution in the original analysis was not. By multivariate analysis, the variables that comprised the final models were the same as those in the original multivariate models, with modest differences in chi-square values.

Figure 4. Kaplan-Meier curves for survival free of cardiac death or MI for the study group separated on the basis of the number of the following adverse prognostic variables associated with this end point: angina during exercise (p = 0.003) and three or more abnormal Tl-201 segments on the postexercise images (p = 0.004). post segs = postexercise segments.



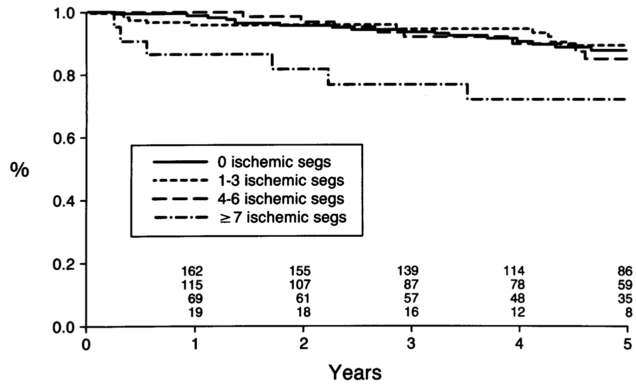


Figure 5. Kaplan-Meier curves for survival free of cardiac death or MI for the study group separated on the basis of the size of the ischemic defect (p = 0.007). segs = segments.

Discussion

Exercise testing is commonly performed after CABG, but there is little evidence supporting the use of testing for prognostic purposes. The present study indicates that exercise

Table 8. Associations Between Global Stress and Reversibility Scores and Outcome

End Point and Variable*	Chi-Square	p Value	HR (95% CI)†
Univariate Analysis			
Total mortality			
Summed stress score	15.9	<0.001	1.05 (1.03–1.08)
Summed reversibility score	<1.0	NS	1.03 (0.91–1.03)
Cardiac death/MI			
Summed stress score	8.8	0.003	1.04 (1.01–1.07)
Summed reversibility score	13.5	<0.001	1.13 (1.06–1.21)
Cardiac death/MI/late PTCA/CABG			
Summed stress score	6.7	0.01	1.03 (1.01–1.06)
Summed reversibility score	6.1	0.01	1.08 (1.02–1.15)
Multivariate Analysis			
Total mortality			
Summed stress score	13.2	<0.001	1.05 (1.01–1.10)
Shorter exercise duration	6.3	0.01	1.23 (1.05–1.44)
Increasing age	5.2	0.02	1.64 (1.07–2.51)
Cardiac death/MI			
Exercise angina score	9.7	0.002	1.82 (1.25–2.65)
Summed stress score	4.9	0.03	1.04 (1.01–1.07)
Cardiac death/MI/late PTCA/CABG			
Chest pain class	9.3	0.002	1.42 (1.13–1.79)
Summed stress score	6.2	0.01	1.04 (1.01–1.07)

*Variables not shown were not significantly associated with outcome (see text for details). †Hazard ratio (HR) is for a decrease in summed stress score and for an increase in summed reversibility score. CI = confidence interval; other abbreviations as in Tables 1 and 4.

Tl-201 imaging performed relatively early after CABG can provide clinically meaningful risk stratification. The absolute difference in 5-year survival rate free of cardiac death or MI was 22% between low and high risk subgroups (Fig. 4).

Tl-201 variables. The only variable independently predictive of all three end points was the number of abnormal Tl-201 segments on the postexercise images. This variable reflects the extent of both myocardial ischemia and infarction. It more likely identifies patients with reduced left ventricular function than variables that measure ischemia alone. Patients with reduced left ventricular function preoperatively have the greatest relative improvement in survival after CABG, but their absolute survival rate still remains lower than that of patients with normal preoperative left ventricular function (27,28).

Tl-201 variables measuring only ischemia contained less prognostic information. Some Tl-201 prognostic studies of patients without previous CABG have reported that the most important independent variable was the number of reversible defects (29–31), but others have found that the most important variable was the number of defects on the postexercise images (32,33). There are several potential explanations as to why ischemia alone was not a stronger predictor of outcome in the present study. 1) The majority of the ischemic defects were small. 2) Redistribution was associated with performance of early revascularization. Clinicians in general are more likely to intervene in patients with ischemia. If ischemia is a marker of high risk, then censoring these patients from analysis at the time of early revascularization would reduce the ability of ischemia to predict future cardiac events. 3) Some patients who did not undergo Tl-201 reinjection before delayed imaging may have had ischemia that was not detected and, conversely, reinjection may have masked ischemia in some patients in whom it was present. The prognostic value of the extent of ischemia was similar in patients who underwent reinjection and those who did not, suggesting that reinjection did not have a major impact on the results of the present study. Nonetheless, the possibility cannot be excluded that ischemia may have shown a stronger association with outcome had all patients undergone delayed imaging followed by reinjection imaging.

The Tl-201 variables that were prospectively selected for analysis at the beginning of the study present were on the basis of the available published reports showing that the extent of a perfusion defect rather than its severity is a stronger prognostic variable (23). Recent publications (15,24) have demonstrated the prognostic value of summed stress and reversibility scores, which reflect both the extent and severity of a perfusion defect. The results of the post hoc univariate analysis indicated a modestly stronger association between these variables and outcome than the variables measuring only the extent of the defect in the original analysis. However, the multivariate models were qualitatively the same, and the chi-square values for the variables in the models were similar. These results suggest that the prognostic information contained in the summed stress and reversibility scores is similar to that provided by variables measuring only the extent of a defect.

There were other notable findings concerning the Tl-201 images. Ischemia proximal to graft insertion was not predictive of outcome. Increased Tl-201 lung uptake was not significantly associated with any outcome end point. This variable was also associated with early revascularization, possibly reducing its prognostic value. Finally, the prognosis for patients with normal Tl-201 images was excellent, with an annual hard cardiac event rate of 1.6%, only slightly higher than the annual risk of 0.9% for patients without a previous CABG (23).

Exercise and clinical variables. Exercise duration was predictive of total mortality, and exercise angina score was predictive of the end point of cardiac death or MI, consistent with earlier studies (12,22). Clinical variables contained little independent prognostic information. Specifically, chest pain class was not associated with overall mortality or a hard cardiac event, indicating that outcome for these end points was the same for patients who were asymptomatic or symptomatic.

Other prognostic exercise studies after CABG. Of the three studies using standard treadmill testing (10–12), only the study by Weiner et al. (12) reported positive results. Two studies (13,14) found that exercise left ventricular ejection fraction measured by radionuclide angiography was predictive of future events. Only one study has examined the prognostic value of Tl-201 imaging after CABG. Palmas et al. (15) reported that a summed reversibility score and increased lung uptake were the most important Tl-201 variables. Notably, all their patients were tested at least 5 years after CABG, and only 15% had internal mammary grafts. Although the importance of individual variables differed between their study and ours, both studies demonstrate that exercise Tl-201 imaging after CABG does have prognostic value.

Study limitations. The major limitations of this study include retrospective design and patient selection bias. Because patients were referred for testing at the discretion of their primary physicians, there are unknown issues affecting the selection process, especially in view of the fact that a much larger number of patients underwent CABG at this institution during this time period. The results of this study may not be reproducible in an unselected patient cohort. Although the number of variables selected for analysis was intentionally limited, the possibility that a spurious association was detected cannot be excluded.

Implications. This study requires confirmation and prospective validation before these findings can be widely applied to clinical management of patients. In the absence of such data, some conclusions seem reasonable. Patients with high risk study results should probably undergo coronary angiography if they are suitable candidates for further revascularization attempts. Patients with only a small perfusion defect generally would not warrant further evaluation solely on the basis of this finding. A prospective, randomized trial is necessary to address the important clinical questions concerning which patients should undergo exercise Tl-201 imaging after CABG, at what intervals testing should be performed and whether such a practice is cost-effective.

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